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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/891,138	06/25/2001	Daniel Chi-Hong Lin	018781-006210US	8826

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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/891,138	LIN ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-7,13,15,18,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-7,13,15,18,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-3,5-7,13,15,18,30 and 31* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Amendment and Response filed 15 October 2003 has been received and entered in full. Claims 4, 8-12, 14, 16, 17, 19-20, and 32-67 have been cancelled. Claims 1, 5-7, 13, 15, 18, and 30 have been amended.

2. The Request to Correct Inventorship under 37 C.F.R. §1.48(b) filed 15 October 2003 has been received and is hereby *granted*. The Application Data Sheet filed 15 October 2003 lists Daniel Chi-Hong Lin of Walnut Creek California as the sole Inventor.

3. The Declaration under 37 C.F.R. §1.132 by Daniel Lin filed 15 October 2003 has been received and taken into consideration.

4. The Petition under 37 C.F.R. §1.137(b) to Revive an Unintentionally Abandoned Application filed 28 October 2003 was *granted* on 5 November 2003. The Amendment and Response filed on 15 October 2003 is considered timely.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

6. The Objection to the Specification as set forth at ¶3-4 pp. 3 in the previous Office Action (15 April 2003) is *withdrawn* in view of Applicant's amendments (15 October 2003).

7. The Rejection of claim **18** under §112 ¶2 as set forth at ¶16 pp. 16 in the previous Office Action (15 April 2003) is *withdrawn* in view of Applicant's amendments (15 October 2003).

Claim Rejections - 35 USC §101 and § 112

8. Claims **1-3, 5-7, 13, 15, 18, 30,** and **31** are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a well asserted utility or a well established utility for the reasons at ¶5-8 pp. 3-12 in the previous Office Action (15 April 2003).

9. Claims **1-3, 5-7, 13, 15, 18, 30,** and **31** are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a well asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention for the reasons at ¶9-10 pp. 13-14 in the previous Office Action (15 April 2003).

10. The Declaration under 37 C.F.R. §1.132 by Daniel Lin filed 15 October 2003 teaches that SEQ ID NO: 1 encodes SEQ ID NO: 2 which has activity to increase in intracellular calcium (*in vitro*). It has not been established what SEQ ID NO: 2 is nor has it been established thus not satisfying the requirements of specific and substantial. The Specification must establish which G-protein coupled receptor (GPCR) it is (with at least 7000 known). Also the Specification must establish what the properties of the claimed GPCR are. The assay as presented only shows in increase in intracellular calcium which may come from any number of internal calcium stores (such as the mitochondria). Also the declaration is not sufficient to overcome the rejection because so many GPCRs will cause changes in intracellular Ca^{2+} when generally stimulated. The data (presented in the Declaration under 37 C.F.R. §1.132 by Daniel Lin filed 15 October 2003) shows that the claimed GPCR is an active receptor but does not reveal anything specific about the

receptor, such as its tissue of origin. Asserted utility is thus not specific. It is also not substantial, as further research is required to determine how to use the claimed receptor.

11. Concerning Applicant's response, argument does not replace evidence where evidence is necessary (MPEP §2145). While the Declaration under 37 C.F.R. §1.132 by Daniel Lin filed 15 October 2003 provides evidence that SEQ ID NO: 1 encodes a protein which responds to succinic acid stimulation, a GPCR with succinic acid as its ligand is not supported by the Specification as filed. Therefore the Declaration under 37 C.F.R. §1.132 by Daniel Lin filed 15 October 2003 is insufficient to meet the utility requirements (credible, specific, and substantial). It is noted that any additional evidence must be supported fully by the Specification (such as the ligand specificity, the tissue of origin, etc.) Therefore the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration.

12. As it stands, the claims remain rejected under 35 U.S.C. §101 and §112 ¶1 for lack of a specific and substantial utility (the utility assertion is credible as GPCRs do exist).

13. On the lack on enablement, the claims are drawn very broadly to any fragment or sequence homologue of SEQ ID NO: 1 and the polypeptide encoded therein which is at

least 25 contiguous amino acids long. The language of said claims encompasses fragments, derivatives, muteins, and sequence variants of SEQ ID NO: 1.

14. The specification teaches that SEQ ID NO: 1 encodes SEQ ID NO: 2.

15. The assay performed in the Declaration under 37 C.F.R. §1.132 by Daniel Lin filed 15 October 2003 teaches the SEQ ID NO: 1 responds to succinic acid as a ligand.

16. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to make or use any fragments, derivatives, muteins, and sequence variants of SEQ ID NO: 1.

17. The specification fails to provide any guidance for the successful cloning and expression of any fragments, derivatives, muteins, and sequence variants of SEQ ID NO: 1. Since the resolution of the various complications in regards to protein activity as highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations fragments, derivatives, muteins, and sequence variants of SEQ ID NO: 1 to correlate with full-length SEQ ID NO: 1. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

18. Additionally, a person skilled in the art would recognize that predicting the efficacy of using fragments, derivatives, muteins, and sequence variants of SEQ ID NO: 1 based solely on its performance suggestion (invitation to experiment) is highly problematic (see MPEP §2164.03). Thus, although the specification prophetically

considers and discloses general methodologies of using fragments, derivatives, muteins, and sequence variants of SEQ ID NO: 1, such a disclosure would not be considered enabling since the state of protein biochemistry is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

19. The following references are cited herein to illustrate the state of the art of protein biochemistry.

20. GPCRs or Serpentine receptors have by definition 7 transmembrane domains. Each transmembrane domain consists of an a-helix which is a minimum of 20 amino acids, connecting each TMD is a open formation polypeptide chain of about 10 amino acids (forming both extracellular and intracellular loops). Therefore at minimum a true GPCR would have 230 residues. This excludes any binding domains, secondary messenger docking domains, catalytic domains, and the like. Therefore it is physically impossible to have a GPCR with only 25 amino acids, or 100, or 200 {see Stadel *et al.* (November 1997) "Orphan G-protein-coupled receptors: a neglected opportunity for pioneer drug discovery." TiPS **18**: 430-437 (Figure 1)}.

21. Regarding derivatives and fragments of SEQ ID NO: 1 and 2, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural

determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional

configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

22. Applicant traverses this rejection on the following grounds: **(a)** it is well settled in the biotechnology art that routine screening of even large numbers of samples is not

undue experimentation when a probability of success exists, **(b)** the Specification provides guidance to make the claimed sequences based on structural properties and guidance for performing assays to assess the function of the sequences, **(c)** the Specification provides amply disclosure for screening nucleic acids encoding GPCRs having the claimed structural and functional characteristics, and **(d)** a rejection for undue breadth is inappropriate where one of skill could readily determine any one of the claimed embodiments (MPEP §2168.08).

23. Applicant's arguments have been taken into consideration and are not found persuasive for the following reasons.

24. On "**(a)**", the breadth of the claims as currently presented constitutes an invitation to experiment. Insufficient guidance is presented to support the undertaking of screening, isolating, and characterizing all the fragments and sequence derivatives currently claimed. Further since SEQ ID NO: 1 fails to meet the utility requirement no success can be expected as extensive research is required to first characterize SEQ ID NO: 1 before under taking extensive experimentation to screen, isolate, and characterize all of the fragments and sequence variants claimed.

25. On "**(b)**", the claims as currently presented constitute an invitation to experiment. Insufficient guidance is presented to support the undertaking of screening, isolating, and characterizing all the fragments and sequence derivatives currently claimed. The Applicant provides only prophetic consideration of what should be done, lists a battery of assays available to the artisan, and suggests possible results. Further since SEQ ID NO: 1 fails to meet the utility requirement as extensive research is required to first characterize

SEQ ID NO: 1 before under taking extensive experimentation to screen, isolate, and characterize all of the fragments and sequence variants claimed.

26. On "**(c)**", SEQ ID NO: 1 fails to meet the utility requirement extensive research is required to first characterize SEQ ID NO: 1 before under taking extensive experimentation to screen, isolate, and characterize all of the fragments and sequence variants claimed. Therefore the claims as currently presented constitute an invitation to experiment. No concrete structure or functional parameters are present. Thus the skilled artisan must isolate and characterize SEQ ID NO: 1 and then undertake further experimentation in the absence of guidance to isolate and characterize the myriad of fragments and sequence variants claimed.

27. On "**(d)**", the MPEP states that a claim may have non-enabled embodiments. But as discussed above the instant claims have no enabled embodiments. The Examiner was unable to locate MPEP §2168.08 in the latest version of the USPTO's MPEP updated February 2003.

28. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from prophetic suggestion to make and use fragments, derivatives, muteins, and sequence variants of SEQ ID NO: 1 as exemplified in the references herein.

29. Claims **1-3, 5-7, 13, 15, 18, 30,** and **31** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s),

at the time the application was filed, had possession of the claimed invention for the reasons as set forth at ¶11-15 pp. 14-15 in the previous Office Action (15 April 2003).

30. Applicant traverses this rejection on the following grounds: **(a)** the claim language defines physical and structural properties of the invention as explicitly required by the court in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997), **(b)** Example 14 of the Revised Written Description Examination Guidelines, Federal Register, Vol. 66, No. 4, 1099, January 5, 2001 supports claiming sequence variants, and **(c)** Example 9 of the Revised Written Description Examination Guidelines, Federal Register, Vol. 66, No. 4, 1099, January 5, 2001 supports claiming sequences which hybridize to the claimed sequence.

31. Applicant's arguments have been taken into consideration and are not found persuasive for the following reasons.

32. On "**(a)**", in the instant case Applicant is claiming further sequence derivations of an invention without utility that is not enabled. This does not match the fact pattern of in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997) wherein UC sought greater breadth of claims when they only possessed a single species of a much larger genus. The Court ruled the claims invalid under 35 U.S.C. §112 ¶1, because the specification, although it provided an adequate written description of rat cDNA, did not provide an adequate written description of the cDNA required by the asserted claims. Therefore the instant claims recite a percent identity, an insufficient structure parameter and one with no functional value, with a disclose sequence with no utility that is not enabled and thus does not satisfy the written description requirement.

33. On "**(b)**", again the fact pattern does not match the instant application where the claims encompass sequence derivations of an invention without utility that is not enabled. In the instant case no set assay which may be performed to valid the identity of the receptor. Further Example 14 covers enzymes which are known to possess strongly conserved active regions and other poorly conserved regions which are amenable to mutation. This is not the case with GPCRs especially the one instantly claimed as not guidance to which regions, residues, or stretches of amino acids are amendable to mutation and variance.

34. On "**(c)**", the instant applicant is drawn to a sequence that has not utility and is not enabled. Hybridization itself it arbitrary and does not sufficiently disclose which sequences will be so identified. Further as noted above any sequences which hybridize to the claimed sequence will require extensive experimentation to characterize them as the instant sequence is has not meet the utility requirement and is not enabled. In addition, hybridization is insufficient basis to establish a function for the sequences so claimed.

35. Finally, concerning Applicant's response, argument does not replace evidence where evidence is necessary (MPEP §2145). Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. And as noted above GPCRs or Serpentine receptors have by definition 7 transmembrane domains. Each transmembrane domain consists of an a-helix which is a minimum of 20 amino acids, connecting each TMD is a open formation polypeptide chain of about 10 amino acids (forming both extracellular and intracellular loops). Therefore at minimum a true GPCR would have 230 residues. This excludes any binding domains, secondary messenger docking domains, catalytic domains, and the like. Therefore it is physically

impossible to have a GPCR with only 25 amino acids, or 100, or 200{see Stadel *et al.* (November 1997) "Orphan G-protein-coupled receptors: a neglected opportunity for pioneer drug discovery." TiPS **18**: 430-437 (Figure 1)}.

Summary

36. No claims are allowed.

37. **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

38. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on **(571) 272-0887**. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

CJN
February 11, 2004